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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



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(54) Title: PHARMACEUTICAL COMPOUNDS

A—B—N(O)_s (I) (57) Abstract: Compounds or their salts of general formula (I): A-B-N(O), wherein: s is an integer equal to 1 or 2; A = R-T₁-, wherein R is the drug radical and T₁ = (CO)_t or (X)_t, wherein X = O, S, NR_{1c}, R_{1c} is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -T_B-X₂-O- wherein T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above defined; X₂, bivalent radical, is such that the precursor drug of A and the precursor of B meet respectively the pharmacological tests described in the description.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/07225

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C219/14 C07C219/30 C07C229/42 C07C233/25 C07D219/10
 C07D295/08 C07D309/30 C07D401/12 C07D471/04 C07D495/04
 C07D499/68 C07H15/252 A61K31/21 //C07D495/00,333:00,213:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 597 847 A (J. A. MATJI, ET AL.) 28 January 1997 (1997-01-28) column 1, line 47 - line 67; example 1	1-13
X	G. CIRINO, ET AL.: "Inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivatives with gastrointestinal sparing properties" BRITISH JOURNAL OF PHARMACOLOGY, vol. 117, no. 7, April 1996 (1996-04), pages 1421-1426, XP000938504 Stockton Press, Basingstoke, GB ISSN: 0007-1188 the whole document	1-13

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

25 October 2001

Date of mailing of the international search report

25 OCT 2001

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/07225

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G. BENONI, ET AL.: "Plasma concentrations and pharmacokinetic parameters of nitrofenac using a simple and sensitive HPLC method" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 84, no. 1, January 1995 (1995-01), pages 93-95, XP002164443 American Pharmaceutical Association, Washington, DC, US ISSN: 0022-3549 the whole document	1-13
X	US 5 861 426 A (P. DEL SOLDATO, ET AL.) 19 January 1999 (1999-01-19) the whole document	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/07225

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6, 11-13 (not searched in part), 7-10 (not searched)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-13 (partially)

Compounds of examples 15 and 21 containing a drug and nitro group linked by a linker derived from 1,4-butanediol, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

2. Claims: 1-13 (partially)

Compounds of examples 9 and 10 containing a drug and nitro group linked by a linker derived from 6-hydroxyhexanoic acid, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

3. Claims: 1-13 (partially)

Compounds of examples 1-4,7,8,11,13,17 and 21 containing a drug and nitro group linked by a linker derived from 4-hydroxybutyric acid, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

4. Claims: 1-13 (partially)

Compounds of examples 5,14,16 and 19 containing a drug and nitro group linked by a linker derived from N-methyldiethanolamine, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

5. Claims: 1-13 (partially)

Compounds of examples 6 and 18 containing a drug and nitro group linked by a linker derived from diethyleneglycol, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

6. Claims: 1-13 (partially)

Compounds of example 12 containing a drug and nitro group linked by a linker derived from thiodiethyleneglycol, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 1-6,11-13 (not searched in part), 7-10 (not searched)

Present claims 1-13 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, present claims 1-13 relate to compounds defined by reference to a desirable characteristic or property, namely that their precursors attain a certain level of anti-oxidative activity evidenced according to test 4A and test 5 (which are elucidated in claim 1) and at least a certain level of at least one of (a) gastrointestinal damage, (b) apoptosis or (c) hepatic damage and/or gastric damage and/or cardiovascular damage evidenced according to tests 1 to 3 (also elucidated in claim 1). Since the combination these properties (pharmacological activity and lower toxicity) is in fact the problem to be solved by the compounds of the present application (see page 5, line 36 - page 6, line 10 of the description), this means that the claimed compounds are defined in terms of their being a solution to this problem.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in examples 1-21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/07225

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